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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,056	01/29/2007	Jun Hu	CSPTAL17.002APC	9259

20995 7590 08/17/2009

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/582,056	HU, JUN	
	Examiner	Art Unit	
	David A. Saunders	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/06, 1/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO REQUIREMENT FOR ELECTION OF SPECIES

Applicant's election of the following species is noted:

A. HLA-I. Claims 1-11 read on this species of the antigen.

B. Prograf (FK506). Claims 1-7, 10-19, 22 and 23 read on this species of immunosuppressant. For the purposes of examination, claim 20 has been withdrawn in this Office action.

C. TGF-beta. Applicant considers that Claims 1-21 and 23 read on this species of cytokine. The examiner does not concur, because instant claims 14 and 16, like claim 22, involve the use of a of a cytokine neutralizing antibody, rather than the use of a cytokine. Thus Claims 1-13, 15, 17-21 and 23 read upon the elected species of TGF-beta.

D. Anti-IL-2. Claims 1-23 read on this species of a neutralizing antibody.

Applicant has traversed the election of species requirement by urging that 'The various species for the terms "antigen", "immunosuppressive agent", "cytokine which can either stimulate or inhibit cell proliferation or activation", and "neutralizing antibodies against the specific cytokines" all possess the same properties known in the art and can perform the same function in the present invention.' These urgings are unconvincing because, if one were given a journal paper which only disclosed instant Examples 1 and 2, one would have been led to consider that the disclosed method is particularly related to addressing a problem pertaining to anomalies involved in the signals obtained from MLC cultures. One would have had no suggestion or motivation to consider a similar assay method that would test for activated lymphocytes that respond to viruses or bacteria. It is only applicant, not the general knowledge in the art, who has recognized that all kinds of antigens would be appropriately used in the instantly claimed method; thus the requirement for election of species A is proper. Likewise, one given a disclosure of only Examples 1 and 2, which use anti-IL-2 as an immunomodulator in the

cultures, would have had no teaching or suggestion to use another one of the diverse array of immunosuppressants, anti-cancer agents, cytokines and anti-cytokines, which would be expected to affect different points in the activation pathways of lymphocytes and thus have differing effects upon the responsiveness of antigen-specific lymphocytes; thus the requirement for election of species B, C and D is proper.

OBJECTION(S) TO DRAWINGS

The drawings are objected to because each of sheets 1-4 has a Chinese character before the Arabic figure number.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

REJECTION(S) UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-19 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing because it refers to plural "lymphocytes" in the preamble and in steps 1) and 2), but it refers to a singular "lymphocyte" in steps 3) and 4). Consistency is required; it is considered that recitation of plural "lymphocytes" would be appropriate throughout the claim.

Claim 1 is unclear because it does not set forth the difference(s) in the components that are to be added to the "test wells" and the "control wells". As far as the examiner can determine, the "control wells" could have "irrelevant antigen(s)" added, instead of the "antigen" used in step 1); see, for example, spec. page 5, lines 18+. Alternatively, the "control wells" could have no antigens added; see, for example, "Group C, control group", which has no added antigenic stimulator cells, as disclosed in Examples 1 and 2. See, also, the "Control group" which has no added purified viral antigen added, as disclosed in Example 3. While the specification may have described what is meant by "control wells", the claim is indefinite, unless it explicitly sets forth the feature(s) which distinguish the components that are to be added to the "test wells" and the "control wells".

Claim 1 is furthermore unclear, because the claim does not state how the "comparing" done in step 4) relates to the purpose of "detecting specificity of activated lymphocytes" that has been set forth in the preamble. It is considered that applicant may be able to overcome by adding a wherein clause, as a conclusion of step 4), such as:

--wherein a weaker activity of the lymphocytes in the test wells than in the control wells is indicative of the existence antigen-specific activated lymphocytes in the test wells.--

The Office considers that the above "wherein" clause would be supported by, for example, spec. page 16, lines 4+; page 22, line 20-page 23, line 3; page 26, lines 25+; page 27, lines 18+; page 28, last 3 lines; page 30, lines 2-8.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential functional cooperative relationships of elements, such omission amounting to a gap between the necessary functional connections. See MPEP § 2172.01. The omitted functional cooperative relationships are: the claim does not explain how the "incubating" of step 3) gives rise to any "detectable signals" that are to be compared in step 4).

Claim 5 is unclear by reciting "activity changes" since it does not state what component used in claim 1 has any changes in "activity", and it does not state what is done to determine any "activity changes". Claim 5 thus recites little that would complete the gap between the necessary functional connections that has been noted supra regarding steps 3) and 4) of claim 1.

In claim 10 "the cytokines which can stimulate cell proliferation" lack antecedent basis, because independent claim 1 has instead referred to "cytokines which can induce [emph. Added] cell proliferation".

Independent claim 12 could be read as providing for the use of a medium, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 12-23 are thus also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). To overcome, it is suggested that applicant recite "A medium for detecting the specificity..." in lieu of "A medium used to detect the specificity..." Applicant must also avoid recitations of "used" in dependent claims 13-17.

In claim 12, it is unclear how many of the additional ingredients listed (each listed ingredient is considered to be what is recited between successive commas) at lines 3-5 must be present in the medium. Is this a Markush group listing, so that only one of the listed ingredients must be present? Alternatively, must all of the ingredients listed at lines 3-5 be present? As far as the examiner can determine, the disclosure would only require that one of the listed components be added; note that, in Examples 1-3, the only added component is a neutralizing antibody against a cytokine (IL-2) which can induce

cell proliferation. Applicant must therefore amend claim 12 so that it reads as a Markush group listing, so that only one of the listed ingredients need be present, in order to not enter new matter.

In claim 14 "the cytokine neutralizing antibody used which can induce cell proliferation" lacks antecedent basis, because independent claim 12 has instead referred to "neutralizing antibodies against the cytokines which can induce cell proliferation". The difference of word order in claim 14 completely changes the intent of what has been set forth in claim 12.

In claim 15 and in claim 23 depending therefrom, "the cytokines which can inhibit mononuclear cell activation" lack antecedent basis, because independent claim 12 has instead referred to "cytokines which can inhibit cell activation".

In claim 18 and in dependent claim 19, the recitations of "the anti-cancer medicaments" and/or of "or inducing tumor cell apoptosis" are unclear, because base claim 13 has only referred to the concentration range of "immunosuppressive agents".

In claim 22 "the cytokines which can stimulate cell proliferation" lack antecedent basis, because independent claim 12 has instead referred to "cytokines which can induce cell proliferation".

In claim 22, line 2, "is" should be –are--, in order to agree with the plural "cytokines" recited in line 1.

In claims 22 and 23, "The method" lacks antecedent basis.

REJECTION(S) UNDER 35 USC 112, FIRST PARAGRAPH

Claims 8 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In each of claims 8 and 18 the Markush group member recited as "other medicaments which are potentially capable of inducing immunosuppressive function or inducing tumor cell apoptosis" is a large subgenus of medicaments which have not been described, except by function. No representative member of such "potentially capable" medicaments has been described, and no direction has been given in the disclosure as to how one would go about finding any members of this subgenus. In short, any "medicaments which are potentially capable" of inducing immunosuppression or of inducing apoptosis, were not known to applicant at the effective filing date of the application, since any "potential" capability remains to be discovered. All materials necessary to practice a claimed invention must have been publicly available as of the filing date. Ex parte Moersch 104 USPQ 122.

REJECTION(S) UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11-12, 15 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamaway et al (US 6,150,121, cited on PTO-892).

Hamaway et al teach a method in which antigen is provided in a medium. In this case the antigen is "particulate" antigen presented on the surfaces of graft-derived

fibroblast-like (GDFL) cells, which bear MHC-class-I antigen (i.e. these cells serve as stimulator cells); see teachings at col. 3, line 61-col. 4, line 9. The medium in which these cells are provided is RPMI containing 15% FCS; see col. 6, lines 2-4.

Hamaway et al teach that a suspension of peripheral blood lymphocytes (PBLs) from a graft recipient is prepared in the same medium, and aliquots of the suspension are then added to wells of a culture plate containing the antigenic GDFL cells. See col. 5, lines 42-67 for the preparation of responder PBLs; see col. 6, lines 5-6 teaching addition of responder PBLs to the wells containing the GDFL cells.

Hamaway et al then add IL-2 diluted in RPMI-15% FCS medium to some of the wells, and they add just the RPMI-15% FCS medium to other wells; see col. 6, lines 6-10. The foregoing wells correspond, respectively, to those of instant Groups B and A, as disclosed in Examples 1-2 (since claim 1 is indefinite by failing to set forth how the "test wells" and "control wells" are to be distinguished, and how one is to conduct the "comparing", the examiner can only compare the prior art with the instant Examples).

Hamaway et al teach that, in like manner, cultures of GDHLs from a 3rd party (control) are prepared (i.e. these cells serve as "irrelevant antigen" stimulator cells). The PBLs from the graft recipient are likewise added to the 3rd party GDHLs. In like manner, Hamaway et al add IL-2 diluted in RPMI-15% FCS medium to some of the wells, and they add just the RPMI-15% FCS medium to other wells; see col. 6, lines 1-14. The foregoing wells correspond, respectively, to those of instant Groups C and D, as disclosed in Examples 1-2.

Hamaway et al then incubate all of the cultures for 3 days, following which they incubate the cultures with ^{3}H thymidine and determine the degree of incorporation of the ^{3}H thymidine by the responder cells, in order to provide "detectable signals". See col. 6, lines 15-32. Hamaway et al then calculate a % response (^{3}H thymidine incorporated by responder cells sans IL-2/ ^{3}H thymidine incorporated by responder cells with IL-2) for the cultures with graft derived stimulator cells and for the cultures with third party derived stimulator cells. A significantly greater IL-2-/IL-2+ response is observed in the cultures with the graft-derived stimulator cells than the cultures with the third party-derived stimulator cells, for the cases in which the responder PBLs are derived from a graft recipient who is rejecting a graft (i.e. the responding PBL sample contains "antigen-specific activated lymphocytes"). See Tables 1 and 2 at cols 7 and 8. Hamaway et al thus "determine the existence of antigen-specific activated lymphocytes by comparing the differences between test wells", as required by step f) of claim 1.

These teachings are sufficient to anticipate, since IL-2 is a "cytokine which can inhibit mononuclear cell activation and proliferation", as evidenced by instant claim 11. From the above, instant claims 1-3, 5 and 11 are anticipated.

Regarding claim 4, note col. 6, lines 7-8. These teachings also clearly anticipate instant composition claims 12, 15 and 23.

Regarding other species of cytokines, note that Hamaway et al teach that IL-4 or TGF-beta (the instantly elected cytokine) can be used in lieu of IL-2 (col. 2, lines 60-62). These teachings apply to claims 11-12 and 23.

Claims 12, 14, 16-17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Stafford et al (6,346,247, cited on PTO-892).

Stafford et al teach the 2-fold serial dilution of an avian anti-IL-2 polyclonal antibody in culture media; see col. 8, lines 55-67. The starting concentration of the antibody is in the range of 20-35 mg/ml; see col. 7, lines 38-39. The avian anti-IL-2 polyclonal antibody has IL-2 neutralizing activity, as taught by Example 3.

In like manner, Stafford et al teach various dilutions of an avian anti-IL-12 polyclonal antibody in culture media; see col. 9, lines 13-42. The concentrations of the avian anti-IL-12 antibody range from 2,500 ug/ml down to 0.032 ug/ml; see col. 9, lines 24-25. The avian anti-IL-12 polyclonal antibody has IL-12 neutralizing activity, as taught by Example 4.

From the above, the claimed medium of instant claims 12 and 22 is anticipated. The taught concentrations of the anti-IL-2 and anti-IL-12 antibodies are consistent with the concentration limits of instant claim 14 and its dependents, claims 16-17. Though the diluted antibodies are used for a propose different from that recited in the preamble of claim 12, anticipation is proper, since any intended use of the medium carries no patentable weight.

Claims 12-13, 18-19 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Karpas et al (5,801,144, cited on PTO-892).

Karpas et al teach the culturing of an HIV-infected leukemia cell line in media which contain the immunosuppressant CsA or FK506. See Example 1. Karpas et al

teach concentrations of 1, 4 or 10 ug/ml were used (e.g. col. 2, lines 13-19; col. 3, lines 6 and 25-27; col. 4, line 54). Thus instant claims 12-13, 18-19 and 21 are anticipated.

Though the diluted immunosuppressants are used for a propose different from that recited in the preamble of claim 12, anticipation is proper, since any intended use of the medium carries no patentable weight.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm and on alternate Fridays. The examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax number where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 8/11/09 DAS

/David A Saunders/

Primary Examiner, Art Unit 1644